

Air Pollution and Cancer: Risk Assessment Methodology and Epidemiological Evidence

Report of a Task Group*

Introduction

This report is the result of an International Symposium on General Air Pollution and Human Health with Special Reference to Long-Term Effects held in Stockholm, March 8-11, 1977. The meeting was organized by the Karolinska Institute through its Department of Environmental Hygiene, which is also a World Health Organization (WHO) Collaborating Centre for Environmental Health Effects, and was sponsored by the Swedish Governmental Committee on Energy and Environment.

The objective of the meeting was to consider current scientific knowledge about carcinogenic substances in air in relation to epidemiological data on lung cancer and available methods for assessing cancer risk from experimental data. The specific questions addressed to the participants of the Symposium were the following.

Can part of the increased incidence of lung cancer in urban communities be related to exposure to air pollutants? If so, is it possible to quantify dose-response relationships after control for smoking habits, occupational exposures and other habitual or socio-economic factors?

Can the approach used for radiation protection standards, i.e., to extrapolate dose-response relationships to low doses (for which no epidemiological evidence exists), be applied to combustion pollutants? If so, for which pollutants and effects would such an approach appear justified?

Do urban air pollutants contain substances which have proven carcinogenic or mutagenic in animal models, and can such data be used for risk eval-

uations in man?

About 30 scientists from different countries participated in the meeting (Appendix). The World Health Organization, including the International Agency for Research on Cancer, as well as the United Nations Environment Program were represented.

The Symposium was chaired by Dr. Velimir Vouk, WHO, Geneva (acting in his personal capacity). Vice chairmen were Sir Richard Doll, Oxford, and Dr. Norton Nelson, New York, who also chaired the subgroups on epidemiology, and risk assessment methodology, respectively. Dr. Lars Friberg, the Karolinska Institute, acted as scientific secretary of the meeting.

Attached to the report of the Symposium are working papers, submitted by the participants in advance of the meeting, which formed the basis for the discussions. This report, its conclusions and recommendations, is based on discussions held at the Symposium and the working papers. These working papers are published here, in the present issue of this journal. The working papers are generally not referred to individually in this report.

The report has been unanimously agreed upon by the participants of the Symposium. The final responsibility for the editing has been assumed by an editorial committee consisting of the chairman, the two vice chairmen, the scientific secretary and the two rapporteurs, Dr. Rune Cederlöf, Stockholm, and Dr. Bruce Fowler, Research Triangle Park, USA. Pamela Boston, Stockholm, acted as editorial assistant for the committee.

Carcinogenic Components of Air Pollution

Pollutants in urban air that may contribute to the excess incidence in lung cancer are derived from a

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variety of sources. Most result from the combustion of fossil fuels but some may also be produced by industrial processes and some may be specific to particular technologies. In some countries, exposure to pollutants indoors from inadequately flued fires for heating or cooking may be more relevant than outdoor exposures.

Lists of compounds present in air pollution which are known or suspected to be related to lung cancer and which are known to be derived from the processing or combustion of fossil fuels, are presented in the working papers by Friberg-Cederlöf and Natusch.

In assessing the risk presented by potential carcinogens it is important to note that their physical form may play an essential and even determining role. In this regard it has been established that polycyclic organic matter (POM)* in urban atmospheres is contained predominantly in fine particles that are capable of pulmonary deposition. Experimental evidence indicates that under these physical conditions, polyaromatic hydrocarbons are particularly effective in the induction of respiratory tract cancers (1-3).

Combustion of hydrocarbon fuels is liable to produce a wide range of compounds including the POM class. It is generally assumed that the major carcinogenic potential of combustion products is contained in POM. Normally, if the total POM concentration is high then so is that of benzo[a]pyrene (BaP). To this extent BaP can be regarded as a representative indicator of the class. It may not necessarily be a good indicator of the overall POM carcinogenicity of urban air pollution as it has been shown that carcinogenic compounds in POM from different sources do not retain a constant relationship to each other or to BaP. For some specific sources, however, BaP may be regarded as a useful indicator of carcinogenicity.

Risk Assessment Methodology

Dose-Response Relationships

Experience from Radiation Biology. There is no doubt that the science and practice of radio-

logical protection have advanced more than the control of chemical hazards, and it may be useful to consider whether some of the concepts successfully applied in radiological protection, particularly as regards dose-response relations, may be profitably adopted in the protection against environmental pollution. Research into the biological effects of radiation, e.g., cancer induction, has provided data leading to many different formulations of response as a function of dose. Displayed graphically, these may be straight or curved lines, with or without a maximum and with or without a threshold. In contrast, the usual approach in chemical toxicology has been to assume the existence of a threshold dose, below which there are no observable effects irrespective of the length of exposure. The appropriateness of this assumption for chemical carcinogens and mutagens has been challenged, however.

For purposes of radiological protection, the International Commission on Radiological Protection (4-6) considers that all doses, no matter when or at what rate they are received, are additive. It was realized that this assumption was valid only if an arithmetic plot of response against dose yielded a straight line passing through the origin (after deduction of background). This dose-response relation was evident for the production of mutations and was adopted for all late effects of radiation. Reasons for its adoption were its practicality in managing radiological protection measures and the realization that in most cases it was conservative, that is, it was likely to overestimate the effects of low doses.

When the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) began estimating the risks of stochastic effects of radiation exposure in human beings, it decided to express the results as excess cases of deleterious effect per million persons per year (or per lifetime) per unit absorbed radiation dose. This was arrived at by observing the incidence rate in populations exposed to tens or hundreds of rads of radiation and dividing the excess rate of incidence by the dose. Such a procedure is valid only under the same assumptions about the dose-response relation that ICRP had made. These assumptions were adopted by UNSCEAR for the purpose of estimating risks (7, 8).

The estimates of risks for man had to be made from studies of population groups receiving relatively high doses because the observed effects were of the same type as those occurring spontaneously at lower doses. Having made the estimate at high doses it was then necessary to extrapolate to low doses.

*Throughout this report the term polycyclic organic matter or compounds (POM) is used to apply collectively to those aromatic compounds which have condensed rings and which may contain heteroatoms or have attached substituents. The term polyaromatic hydrocarbon (PAH) is much more restrictive and is used to refer only to hydrocarbons (i.e., condensed-ring aromatics containing only carbon and hydrogen atoms). The term polynuclear aromatic (PNA), which is equivalent to POM, is not employed in this report.

Human data on dose-response relations are scanty and animal data are variable. It has, however, become more likely, on microdosimetric and theoretical grounds, that in the mathematical formulation of the dose-response relationship the frequency of many harmful effects is likely to be represented, up to rather high doses, by the sum of three terms, one being the background frequency, one varying with dose, and the third varying with the square of dose, i.e.,

$$F = a + bD + cD^2 \quad (1)$$

where D is the dose, a is the background frequency, and b and c are constants. In order to indicate that the response declines at very high doses, presumably due to cell death, this expression may be multiplied by an exponential term with a negative exponent which is a function of dose.

This formulation indicates that for low doses the effect is proportional to the dose, while at higher levels it varies as the square of the dose. It is not known, at least for tumor induction, at what dose the linear and quadratic components become equal and the relationship ceases to be predominantly linear. For mutations in experimental systems, this "crossover," with equal contributions from each term, usually appears to occur at between 50 and 100 rad for low LET (linear energy transfer) radiation (9). Assuming that this applies to tumor induction, the slope calculated from response at doses of the order of 100 rads will in some cases overestimate the response per unit dose of radiation at low doses, possibly by a factor of 2-4.

For this reason the procedure just outlined has been criticized by some as being too conservative and demanding too high a price for protection against hazards of nuclear power. This conservatism has been praised by others as being honest by not assuming that safety exists when it cannot be proved.

While in experimental radiobiology it is important to consider all shapes of dose-effect and dose-response curves in order to gain insight into the mechanism at work, in radiological protection the extra precision gained by departing from a linear relation between dose and response is rarely warranted by the quality of data and certainly not of consequence at low doses.

Chemical Carcinogenesis. It is now appropriate to examine the relations between responses and doses of chemical pollutants. Frequently, inadequate attention is given to what is meant by "dose." The nature of the relation between dose

and response will depend on how the dose is measured and expressed. For scientific purposes, the dose should ideally be considered as the concentration of ultimate carcinogen at the site of action in the tissues or cells—measured at all times after its introduction. This will be called the target dose D_t . In studies of stochastic effects it seems most appropriate to define target dose as the time integral of the concentration $C(t)$ of the ultimate carcinogen at its site of action:

$$D_t = \int_0^t C(t) dt \text{ (molar-seconds)} \quad (2)$$

where t is the duration of exposure of the target to the ultimate carcinogen.

It may also be necessary to multiply D_t by some modifying factor to take account of the effects of dose rate or other variables. In the case of primary electrophilic reagents, the target dose is expected to be proportional to the exposure dose, D_{exp} , i.e.

$$D_t = kD_{\text{exp}} \text{ (concentration} \times \text{time)} \quad (3)$$

where k is a constant.

Equation (3) is not generally valid, however, for secondary electrophilic reagents formed metabolically. Since dose-response curves for chemically induced cancer are mostly based on D_{exp} , D_t not being known, great care is required in the interpretation of the dose-response curves for secondary carcinogens.

There have been a relatively small number of experimental studies of the carcinogenicity of chemicals over a wide range of exposure doses. If tumors are induced by a one-hit mechanism the fraction of animals without tumors N/N_0 would be:

$$N/N_0 = e^{-kD_t} \quad (4)$$

where k is a constant and D_t is the target dose.

It is noteworthy (10) that for certain polycyclic organic compounds the relation between doses and responses resembles that for radiation in that it does not deviate significantly from that predicted by equation (4). The same is valid for, e.g., genital tumors induced by *N*-ethyl-*N*-nitrosourea [data from Ivankovic (11)].

Such cases support the idea that for carcinogenic chemicals there is, for small doses from zero, a linear relation between dose and response. Also, certain epidemiological data for human exposures indicate, within limits of error, that a one-hit mechanism may play a part in the induction of cancer (12, 13). A mechanism involving one or more single hits would be in agreement with the

mutation hypothesis for chemically induced cancer (14). Most alkylating agents induce mutations at low doses proportionally to the dose but with a greatly increased yield per unit dose above some critical dose, possibly due to impairment of repair (15).

Since tests for carcinogenicity of chemicals are frequently made with small groups of animals, and hence have low power, it is not surprising to encounter an apparent "threshold" dose with no observed response.

In some animal experiments with benzo[a]pyrene (16-19), lower doses were found to be more effective per unit dose than higher doses, due probably to a more effective metabolic production of ultimate carcinogens at lower doses, which means a departure from Eq. (4). The greater effectiveness of divided doses in producing cancer (20) may also be explained by the same postulate. Thus the linear hypothesis may not be as conservative as has been assumed.

Background levels of both doses and responses are relevant to both ionizing radiation and air pollutants. There are naturally occurring levels of radiation so that there is no zero dose level in any experiment. Some air pollutants also occur naturally, e.g., SO_x, NO_x, PAH, and dust. New man-made chemicals are not present as ambient air pollutants before they are manufactured in quantity but others that have been in use for some time may be ubiquitous. Thus in epidemiological studies we are concerned with dose-response relationships only, where doses and responses are measured in relation to background levels and responses (incremental doses and responses).

Another problem that arises in many epidemiological investigations is that the dose is expressed as an average concentration in some medium such as inspired air or drinking water, and marked departures from the mean for different persons in the population may have overriding importance for the induction of effects.

Factors Influencing the Carcinogenic Response

A number of factors can influence, in varying degrees, the likelihood of a carcinogenic response to given chemical exposures. They include: those factors which control the transport, localization and metabolic activation or inactivation of carcinogens in the organism and thus influence the effective dose of ultimate carcinogen at the molecular level (target dose); the interaction with other carcinogens; the effect of noncarcinogenic agents such as cocarcinogens, promoting agents and inhibitors;

individual susceptibility factors.

Effective Target Dose. It seems probable that some of the variation in the response to a given exposure dose of a chemical carcinogen may be due to the variation of the effective target dose. This implies that the intrinsic cellular reaction of some tissues to the carcinogenic stimulus of a chemical may vary less when related to the target dose than when related to the exposure dose of the whole organism.

It is relatively easy to predict the target dose of penetrating ionizing radiation. The attempt to estimate the target dose of chemical carcinogens for a given tissue becomes increasingly complex in the following four situations: direct-acting carcinogens (not requiring metabolic activation) on directly exposed tissues (e.g., alkylating agents on skin or bronchial epithelium); indirect carcinogens (or procarcinogens, which require metabolic activation) on directly exposed tissues capable of metabolic activation (e.g., PAH on skin or bronchial epithelium); direct-acting carcinogens on indirectly exposed tissues (e.g., alkylating agents on hemopoietic cells); indirect carcinogens on indirectly exposed tissues when the metabolic activation is dependent on the enzymatic steps in other tissues and organs (e.g., aromatic amines metabolized in the liver and acting on the bladder).

The target dose is thus the net consequence of the processes of transport, metabolic activation, and detoxification.

Interaction of Carcinogens and Modifying Factors. In evaluating the total carcinogenic effect of air pollutants, consideration should be given to the interaction of different individual substances and classes of materials. Evidence from human and animal data agrees in suggesting that both additive and synergistic effects can occur as a result of multiple exposures to different types of inhaled carcinogenic materials. Noncarcinogenic substances found in fossil fuel emissions may also affect the dose-response relationships, either by acting as cocarcinogens or by impairing metabolic or transport processes. Epidemiological studies have shown that cigarette smoke acts synergistically with asbestos and with radioactive materials in producing cancer in exposed workers.

There is experimental evidence for several types of interactions between different classes of materials in respiratory carcinogenesis. For example, airborne particulate matter (such as metal oxides, carbon or organic particles) can adsorb, transport and retain carcinogens (such as POM) in the respiratory tract and can modify their action in these target tissues (2, 21-23). Different classes of respiratory carcinogens (such as POM, in conjunction with ni-

trosamines, nitrosamides or radioactive material) can interact to produce a marked potentiation of carcinogenic effects. Limited experimental evidence suggests that systematically acting carcinogens may exert a synergistic effect on the action of carcinogens introduced by the respiratory route (24-27). Sulfur dioxide and probably nitrogen oxides may enhance the carcinogenic effects of POM on the respiratory tract (28). Substances which interfere with the metabolic activation of procarcinogens through induction or inhibition of critical enzymatic activation steps can modify the ability of tissues to respond to a given dose of an inhaled carcinogenic agent (29).

Evaluation of the total carcinogenic effect of a polluted atmosphere, which would account for the interaction of components, is very difficult using presently available test methods. The critical problem is that of assessing the total carcinogenic potential.

It has been suggested that some indication of the total effect of interactions may be obtained by using condensates, particularly in short-term test systems. Such tests, however, would not include consideration of gaseous and volatile materials. If positive results are obtained in such tests, they would indicate the need for more sophisticated analyses. Negative results or quantitative comparisons obtained in this way must be interpreted with great caution.

Individual Variability. Variation in susceptibility to a specific carcinogen among individuals of the same species is important and can influence the shape of the dose-response curve. From a public health standpoint, such variation can be decisive in determining the manner in which control measures are devised, since the sensitivity of highly susceptible groups may be of greater importance than that of the average or general population. Individuals may vary in their ability to metabolize a known carcinogenic compound. Animal experiments show that in the case of POM this variability may be under genetic control. Damage induced in DNA by radiation or by chemical carcinogens may be removed, at least to some extent, by cellular DNA repair mechanisms. The dose-response relationships for carcinogens may be influenced by the nature and extent of the repair processes. Small groups of individuals specially sensitive to environmental carcinogens because of defective DNA repair ability have already been identified.

Other sources of such variation include age, sex, current or prior disease and, of course, exposure to modifying influences stemming from occupation, smoking, and nutritional habits.

Extrapolation from Experimental Systems to Man

Quantitative estimations in man on the basis of data from experimental model systems have to be made with great caution for the following reasons.

Some compounds strongly carcinogenic in one species may be weakly carcinogenic in another. For example, aflatoxin has been found to be an extremely strong carcinogen in rats and probably also in man but negative in adult mice of several strains. Arsenic, accepted as a human carcinogen, has not been shown to be carcinogenic in animals.

Difficulties in using quantitative information obtained in nonmammalian or *in vitro* systems are even greater. For example, there does not appear to be a direct quantitative relationship between the number of mutants induced in the Ames test or the number of sister chromatid exchanges induced in human cells by a compound and its carcinogenic potency. Nitrosamines are only weakly active in the Ames test, while mitomycin C, a possibly weak carcinogen, is the most active compound yet tested in the sister chromatid exchange test.

Clear quantitative data have, however, been obtained for a number of individual compounds in animal tests. In such cases it might be reasonable to assume that, if one can obtain some human data to give an indication of one level at which a specific compound is active in man, the shape of the dose-response curve would be the same as in the animal system and extrapolations could be made to low doses on this basis.

There is also the question of whether it is possible to measure levels of air pollutants in the atmosphere (D_{exp}) and from these make estimates of risk to man. In attempting this, a number of difficulties are encountered, for example: the suitability of the experimental species as a model for man, e.g., whether the activation processes are similar in the experimental species and in man; the difficulty of assessing the dose, by measuring the gross quantity of an air pollutant rather than the quantity of the ultimate carcinogen that reaches the target cell in the target organ; the definition of the human population to which the extrapolation is to apply, with respect to age, sex, special susceptibilities, duration and routes of exposure.

Nevertheless a crude preliminary risk estimate can be made, if one has the information on the quantity of the pollutant inhaled by an average individual human subject, at average exposure and experiments with several species of animals at several sufficiently large and well spaced doses measured in

the same manner as is the exposure of man in order to give estimates of a dose-response relationship if one exists.

Then, by taking as the indicator species for man that species which shows a positive carcinogenic response, one could take the upper limit of that response at the lowest dose, and extrapolate this down to a zero-added dose (control response) using for estimates that small, early part of the curve to which we wish to fit a function of the form:

$$\text{Response} = \text{control response} + b_1D + b_2D^2 + \dots + b_nD^n \quad (5)$$

where the b are constants fitted from the data, and D is the dose of concern. It is necessary to estimate a true zero-dose response. This will require a very large number of animals.

In most cases, D will be quite small, so that the terms in D^2 , D^3 , etc. make very small contributions to the estimated response. The procedures from radiation biology, comparing (for example) $(b_1/b_2) D$ to find those doses at, or below which the first term, b_1D , dominates, could be applicable here.

If this technique is applied to several air pollutants, it might be possible to determine those pollutants, which, because of their low concentrations, make little or virtually no contribution to the total exposure, assuming that man is no more sensitive than the most sensitive experimental species.

It is, of course, possible that man may be the most sensitive species and using any animal data could underestimate the risks. This estimation process may give low risk estimates for one further reason. The interactions of pollutants need to be considered, and the estimation procedures so far developed are not able to forecast interaction effects.

This estimation process could be substantially improved if measurements could be made of the levels of the ultimate carcinogen at the point of activity (perhaps the nucleus of the target cell) both experimentally, and in man, if metabolic data were available showing which species responds most nearly like man, if sufficiently high quality animal experimentation had been made to permit firm estimates of the constants in the Eq. (5), or if measurements of distribution of both exposure and susceptibilities in the population were available.

The system described here should also be applicable to a situation in which the background level of response could result from levels of pollutants currently existing in the atmosphere. For some subgroups in the population this background may be so high that the effect of an incremental dose of pollutants will require using the higher-order terms, b_2D^2 , b_3D^3 , etc. There is also a strong likelihood that

the constants fitted (the b) will be different for different population segments.

In rare cases, data on human groups already exist, usually of exposures of healthy young persons in work situations, from which estimates can be made of the effect of exposures at lower levels to other segments of the population. An example is the exposure of gas workers (30, 31), and roofing workers (32) to benzo[a]pyrene together with many other substances. In using data from work situations, problems arise concerning the possibly greater susceptibilities of children, old persons, etc. and the different modes and durations of exposure.

Epidemiological Evidence

Cancer of the Lung

The interpretation of the evidence which justifies the belief that cancer of the lung can be produced by atmospheric pollution is complicated by the fact that the condition embraces a variety of tumors with different causes. It includes not only tumors of different tissues (tracheal and bronchial mucosa, alveolar epithelium, pleura, and connective tissue), but also different histological types of tumors (e.g., squamous carcinoma, small cell carcinoma, and adenocarcinoma of the bronchial mucosa). In nearly all countries, bronchial carcinoma is very much more common than all other types put together and, for the purposes of this discussion, bronchial carcinoma and lung cancer will be regarded as synonymous. It should be remembered, however, that the data from which epidemiological evidence is derived commonly include all types of lung cancer, and this may be one reason for the diversity of the observed results.

Lung cancer is, in general, more common in urban areas than in the countryside by a factor that varies up to several fold. There are, however, notable exceptions, in that lung cancer is less common than expected in some urban areas and more common in some rural areas. Variation in diagnostic standards and medical facilities may have contributed to the recorded urban-rural difference in the past, but such factors cannot account for the current observations in many countries.

The annual incidence of lung cancer in women in countries where cigarette smoking has only recently, or still not, been adopted on a wide scale is seldom much more than 4 per 100,000 population (standardized for age on the European Standard Population), irrespective of the degree of industrialization, and it seems likely that a figure of this

order may represent the unavoidable basic incidence attributable to "natural causes."

The simple observation that the disease tends to be more common in urban areas is not, by itself, sufficient evidence that the disease is attributable to atmospheric pollution. It might be due to other features associated with urban living such as smoking, drinking, and eating habits, a higher risk of infection, or specific industrial hazards associated with employment. Such factors which may confound the possible effects of ambient air pollution are discussed below.

Confounding Factors. Cigarette smoking is the predominant cause of lung cancer. It tends to be more common in urban areas and must be regarded as part of the explanation of the urban-rural difference. Many attempts have been made to take differences in smoking habits into account, and these have, for the most part, led to the conclusion that differences in smoking habits are not sufficient to account for the observed differences in incidence of lung cancer. The data do not, however, show a consistent pattern.

Estimates of the incidence in nonsmokers are of necessity based on small numbers of cases. Some investigators have found an urban-rural difference among nonsmokers, others have not.

In female smokers, a clearcut urban-rural difference is not, in general, observed. If, however, atmospheric pollution and cigarette smoking acted synergistically, this lack of a consistent difference might be explained by the fact that in most countries women have only recently adopted smoking on a large scale. In contrast, differences have been observed in male smokers according to place of residence, within specified levels of cigarette consumption.

The observations on male cigarette smokers suggest either that factors in the urban environment are independently responsible for some of the urban-rural difference or that carcinogens in cigarette smoke and the ambient air act together to produce the disease. However, some investigators noted that they were not satisfied that the studies which led to these conclusions had adequately allowed for the total history of cigarette smoking. If so, the differences attributed to other urban factors such as air pollution would be overestimated.

Data are not available to permit estimates to be made of the effect of "passive smoking." The possibility has to be considered that, in crowded conditions, smoke from other people's cigarettes might periodically pollute the ambient air to the same degree as many other pollutants. Pollution by "passive smoking" is, however, unlikely to make a ma-

terial contribution to the urban-rural difference.

Recent work has suggested that vitamin A deficiency might increase susceptibility to the development of squamous carcinoma of the bronchi (33, 34). The evidence for such an effect is incomplete, but it is thought-provoking and needs to be followed up. There is no reason to suppose that either vitamin A deficiency or any other dietetic factor contributes appreciably to the urban factor in the production of lung cancer.

Several urban occupations involve an increased risk of lung cancer because they result in exposure to large amounts of specific carcinogens at the place of work. Measurements of the concentration of the carcinogens in the inspired air and of the corresponding incidence of the associated disease provide information which may be useful in estimating the effect of ambient atmospheric pollution. The number of people employed in these occupations is too small for known specific occupational hazards to account for more than a small part of the mortality from lung cancer in most urban areas.

There is at present no evidence indicating that the consumption of alcohol, prevalence of specific infections, or genetic differences in susceptibility are likely to contribute to the urban-rural difference in the incidence of lung cancer.

Another factor which may have to be considered in countries with cold climates, where houses have low ventilation rates, is the level of radon gas. This may be between 500-10,000 pCi/m³ depending upon the ventilation rate and the type of building material. Exposure to radon and its daughter products needs to be considered as a potentially significant contributor to the cause of lung cancer, but there is at present no evidence as to whether it contributes to the urban-rural difference.

In summary, the only factors associated with urban life that are likely to account for much of the urban-rural difference are smoking habits, atmospheric pollution, and in some localities, special hazards associated with particular industries.

Evaluation of Risks from Air Pollution. Comparison of the incidence of, or the mortality from, lung cancer in different urban areas, in different states of the USA, in different parts of several other countries and at different times in relation to recorded measurements of the concentration of BaP in the ambient air, taking into account (by one means or another) variations in cigarette consumption, has led some investigators to conclude that the lung cancer death rate in men increases by approximately 5% for each increment of pollution as indicated by 1 ng BaP/m³.

This estimate should be regarded as an upper limit of the possible effect of atmospheric pollution.

Reasons for questioning the quantitative value of the estimate include: the inadequacy of the measurements used to characterize smoking histories (in particular the use of regional consumption data for both sexes combined and the lack of information about differences in past habits, including the age at which smoking began); the inadequacy of a few measures of BaP to represent exposures of large populations over long periods (in particular the lack of data for levels of pollution 30 years or more ago which may be more relevant than present levels in view of the long latent period that is characteristic of many forms of cancer); the much lower estimate derived from observations in women; the unreasonably high figure for the amount of lung cancer attributable to pollution that would have been predicted for many urban areas, particularly in the U.K.; the relatively small occupational risk observed in some groups of workers who were exposed in the course of their work to concentrations of BaP several hundred times higher than that recorded in urban air.

Nevertheless, the data for men working in industries where they were exposed to the combustion products of coal confirm that these products could cause cancer of the lung.

Small amounts of radioactive substances are released by the combustion of fossil fuels. The dose received by the population from this source is so small in comparison with that received from natural background sources that the potential number of cases of lung cancer produced by it is negligible.

Taking into consideration all available evidence, including epidemiological data, experimental studies and the presence of carcinogenic substances in the ambient air, the most reasonable conclusion in the light of present knowledge is that combustion products of fossil fuels in ambient air, probably acting together with cigarette smoke, have been responsible for cases of lung cancer in large urban areas, the numbers produced being of the order of 5–10 cases per 100,000 males per year (European Standard Population). The actual rate will vary from place to place and from time to time, depending on local conditions over the previous few decades. These numbers are tentative estimates, subject to change as and when more data on dose-response relations within different populations become available.

Other Cancers

Observations from many countries have also shown higher incidence rates for many other types of cancer in urban areas as compared to rural areas. Age-adjusted cancer mortality rates among white

men in the United States during 1950–1969 showed urban-rural ratios of 1.5 or above for twelve types of cancer out of 32 (37). Only five ratios were below unity. The picture for women was similar. Sites with high ratios included esophagus, larynx, mouth and throat, rectum, nasopharynx and bladder, several of which are known to relate quite strongly to smoking. Those types that were less common in towns included cancers of the prostate, testis, eye and skin (other than melanoma).

It is not possible to make any detailed assessment of the causal role of air pollution for cancers other than that of the lung. However, even if occupation as well as smoking, drinking, and several other features of life style may explain a major part of the excess deaths, air pollution can not be dismissed as a possible contributory cause. Occupational studies may, in the future, help to indicate whether part of the incidence of any of these cancers can be attributed to atmospheric pollution.

Conclusions

Composition of Urban Air Pollution

Chemical agents derived from the use of fossil fuels and known to be carcinogenic (or cocarcinogenic) are present at higher levels in urban than in rural atmospheres.

Approximate concentration ranges have been established for most of the known carcinogens in urban air although further measurements are required of more recently discovered carcinogens to establish their concentration and their physical and chemical form.

There is a need for new and improved analytical methods for the routine measurements of compounds other than benzo[a]pyrene for future epidemiological studies.

Benzo[a]pyrene may be a valuable indicator of carcinogenicity in the emissions from some specific sources but can not be regarded as a generally adequate indicator of carcinogenic risk of air pollution, and the development and use of other indicators besides BaP are desirable.

Risk Assessment Methodology

If a substance has been shown to be carcinogenic in an adequate animal test system it should normally be dealt with as if it had been shown to be carcinogenic in man, unless adequate epidemiological evidence exists to the contrary. In borderline cases, error should be on the side of safety.

Knowledge of the existence of possible interac-

tions of different components of air pollution—which may result in marked synergistic effects—implies that great caution should be exerted in interpreting observations based on the effects of single factors or partial mixtures such as condensates.

Positive results with a substance in combination of appropriate short-term bioassays should be taken as suggestive of possible carcinogenicity.

In considering protection of human populations, and in the absence of firm evidence to the contrary, it is not justified to assume a "threshold," i.e., that there is a dose below which no response is obtained.

In the absence of relevant dose-response data, the most appropriate way to estimate the risk of lung cancer is to assume that it will be directly proportional to the increase in dose. For small added doses, a simple linear dose-response curve, as used in radiation carcinogenesis, is appropriate. For larger added doses, or special population groups already at high risk, other forms of relationship may need to be considered.

For operational purposes in the absence of better data, it may be necessary to make crude estimates of the risk of carcinogenic air pollutants to man from experimental data on animals.

Epidemiological Evidence

Lung cancer is, in general, more common in urban than in rural areas.

Cigarette smoking is the predominant cause of lung cancer and an important component of urban-rural differences.

Specific occupation and other aspects of urban life such as nutrition and alcohol consumption are not in general important as causes of the urban-rural differences in terms of absolute numbers, except perhaps in some special localities.

Combustion products of fossil fuels in ambient air, probably acting together with cigarette smoke, have been responsible for cases of lung cancer in large urban areas, the numbers produced being of the order of 5–10 cases per 100,000 males per year. The actual rate will vary from place to place and from time to time, depending on local conditions over the previous few decades.

Well documented urban-rural differences have been described for cancers in other organs, but the role of air pollution in determining such differences could not be evaluated.

Recommendations

Composition of Urban Air Pollution

Further monitoring studies of potential car-

cinogens and cocarcinogens in urban and rural atmospheres should be made.

There is a need to have better indicators of the carcinogenicity of air pollutants, than are now available.

Further studies should be undertaken to establish the ways in which carcinogens are physically and chemically associated with airborne particles and how such associations may influence their carcinogenic activity.

Risk Assessment Methodology

Studies using a variety of bioassays should be undertaken to define the carcinogenic activity of individual air pollutants, with particular attention being paid to the relationship between target dose and exposure dose. The methods used should include animal studies, and a battery of appropriate short-term biological and chemical reactivity tests, including electrophilic activity.

Experimental studies on exposure to natural and synthetic mixtures of air pollutants should be undertaken in order to develop test procedures which can be used to assess the total carcinogenic potential of atmospheric pollution.

Epidemiological Evidence

Further and more detailed epidemiological studies are needed to take into account both host characteristics and environmental factors. Of paramount importance would be to consider, in addition to the outdoor air quality and smoking history, such factors as occupational exposure and indoor air pollution from cooking, heating, aerosol sprays, and other people's smoking.

Efforts should be made to identify high risk groups within the population who may be especially susceptible to developing lung cancer.

The urban-rural differences for lung cancer are not consistent under all circumstances, and situations where they are most atypical should be studied to provide clues to the further understanding of the etiology of the disease.

The reasons for the urban-rural differences for other forms of cancer need to be elucidated.

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